

# Current perspectives on the etiology and manifestation of the “silent” component of the Female Athlete Triad

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**Abstract:** The Female Athlete Triad (Triad) represents a syndrome of three interrelated conditions that originate from chronically inadequate energy intake to compensate for energy expenditure; this environment results in insufficient stored energy to maintain physiological processes, a condition known as low energy availability. The physiological adaptations associated with low energy availability, in turn, contribute to menstrual cycle disturbances. The downstream effects of both low energy availability and suppressed estrogen concentrations synergistically impair bone health, leading to low bone mineral density, compromised bone structure and microarchitecture, and ultimately, a decrease in bone strength. Unlike the other components of the Triad, poor bone health often does not have overt symptoms, and therefore develops silently, unbeknownst to the athlete. Compromised bone health among female athletes increases the risk of fracture throughout the lifespan, highlighting the long-term health consequences of the Triad. The purpose of this review is to examine the current state of Triad research related to the third component of the Triad, ie, poor bone health, in an effort to summarize what we know, what we are learning, and what remains unknown.

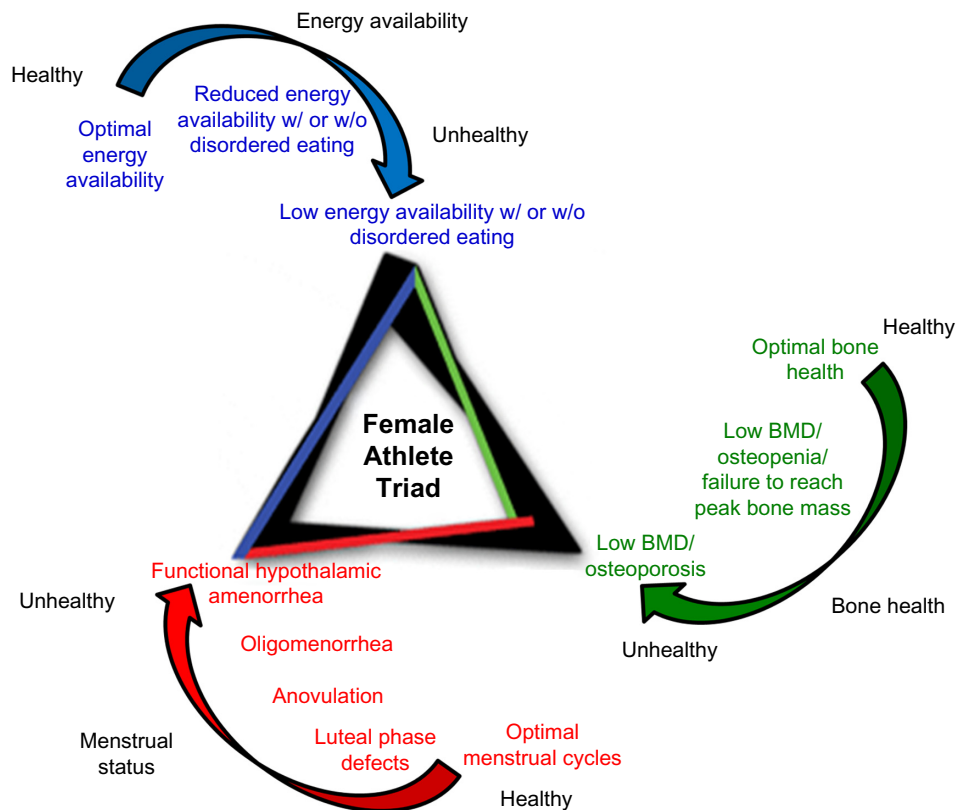
**Keywords:** female athlete Triad, bone health, treatment

## Introduction

Although habitual exercise is intrinsically beneficial to the health and well-being of girls and women, an imbalance between energy intake and expenditure, ie, energy expenditure that chronically exceeds energy intake, leads to physiological adaptations to conserve fuel, which ultimately contributes to clinically identifiable health consequences.<sup>1,2</sup> The health consequences from the energy deficit are collectively referred to as the Female Athlete Triad (Triad), a syndrome composed of the following three interrelated conditions: low energy availability, menstrual dysfunction, and poor bone health (Figure 1).<sup>2</sup> Among female athletes presenting with one or more components of the Triad, compromised bone mass and microarchitecture,<sup>3</sup> which may increase the risk of fracture throughout the lifespan,<sup>2,4-6</sup> and diminished cardiovascular health, as evidenced by impaired endothelial function and an unfavorable lipid profile,<sup>7,8</sup> may also be observed. Notably, the presence of one or more conditions of the Triad has been identified in both elite and recreational athletes ranging in age from adolescents to young adults.<sup>9,10</sup>

Energy availability is defined as the amount of energy available for physiological processes and activities of daily living after subtracting out the energy used for exercise training<sup>11</sup> and is calculated as follows: (energy intake – exercise energy expenditure)/kg lean body mass.<sup>12,13</sup> Low energy availability typically serves as the source of the other

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**Figure 1** Spectra of the Female Athlete Triad. The three interrelated conditions of the Triad include low energy availability, menstrual dysfunction, and poor bone health. Each of these conditions may occur anywhere along a continuum from optimal health to a severe clinical endpoint.

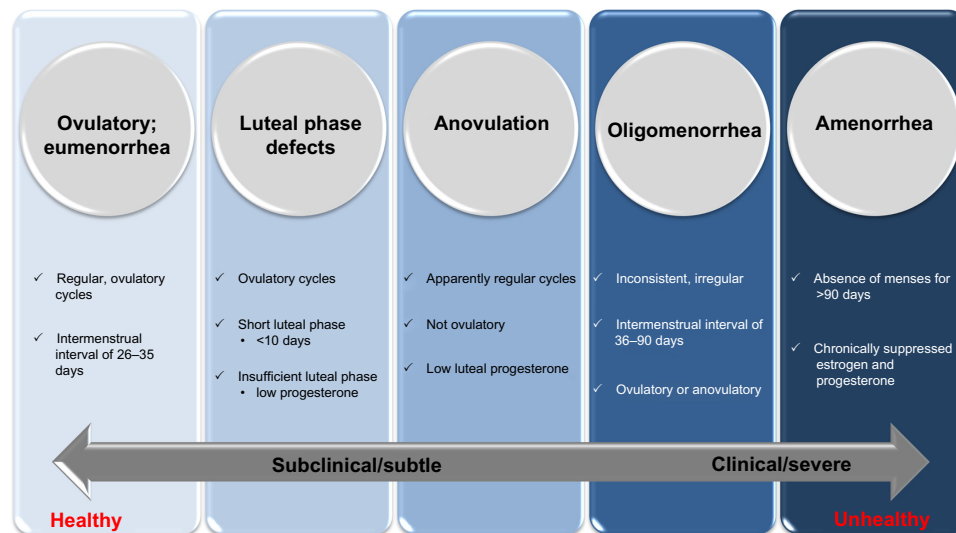
**Abbreviations:** BMD, bone mineral density; w/, with; w/o, without.

two Triad components due to 1) its independent negative effects on reproductive function<sup>12–14</sup> and bone health<sup>15</sup> and 2) the detrimental effects that reproductive dysfunction caused by low energy availability has on bone health.<sup>16,17</sup> It is often accompanied by energy conservation that is characterized by a decrease in resting energy expenditure<sup>14</sup> and circulating concentrations of total triiodothyronine,<sup>14</sup> insulin-like growth factor-1,<sup>18</sup> and leptin,<sup>19</sup> and an increase in ghrelin<sup>14,19,20</sup> and peptide YY.<sup>21</sup> Via neuroendocrine mechanisms, these metabolic adaptations can impair reproductive function and skeletal health.<sup>22–25</sup>

The menstrual function of a female athlete exists on a continuum (Figure 2) from optimal eumenorrheic and ovulatory cycles (26–35 days in length) to amenorrhea, defined as the absence of menses for at least 3 months (secondary amenorrhea)<sup>1,26</sup> or the failure to achieve menarche by the age of 15 years (primary amenorrhea).<sup>27</sup> Under conditions of low energy availability, the hypothalamic–pituitary–ovarian axis is suppressed, most likely mediated through neural signals activated by reduced availability of metabolic fuels and altered concentrations of metabolic hormones.<sup>20–22,24,28,29</sup> These neuroendocrine signals that indicate an energy-deficient state

and a lack of available energy for all physiological processes disrupt the secretion of gonadotropin-releasing hormone from the hypothalamus,<sup>1,20,24</sup> which in turn leads to altered secretion of gonadotropins from the anterior pituitary<sup>13,30–34</sup> and suppressed production of the steroid hormones, estrogen and progesterone, from the ovaries.<sup>13,14,17,35</sup> This cascade of altered reproductive hormones initiates a range of menstrual cycle disturbances from subtle to severe. Subtle menstrual cycle disturbances, which are also known as subclinical menstrual disturbances because they occur in the face of apparently regular cycles, encompass luteal phase defects and anovulation.<sup>26</sup> Severe menstrual cycle disturbances are clinically identifiable due to changes in cycle length, and include oligomenorrhea, which is characterized by long (36–90 days) and inconsistent menstrual cycles, and amenorrhea.<sup>26</sup> Amenorrhea caused by an energy deficit is referred to as functional hypothalamic amenorrhea; it is a result of a functional disorder of the hypothalamus characterized by hypothalamic suppression in the absence of a change in the structure of the hypothalamus.<sup>27,36</sup>

Low energy availability has also been identified as a determinant of bone health due to both energy-related and



**Figure 2** Continuum of menstrual cycle disturbances.

**Notes:** On the far left of the continuum is optimal menstrual health, which is characterized by regular ovulatory menstrual cycles that are 26–35 days in length. The subclinical/subtle menstrual cycle disturbances include luteal phase defects and anovulation, which represent the least severe disturbances. Menstrual cycles with a luteal phase defect are ovulatory but characterized by a short luteal phase and/or insufficient progesterone production during the luteal phase. Menstrual cycles in which ovulation does not occur and progesterone concentrations are notably low are called anovulatory cycles. It must be noted that cycles that have a luteal phase defect or are anovulatory frequently appear to be regular cycles due to intermenstrual intervals of normal length. The clinical/severe menstrual cycle disturbances include oligomenorrhea which is characterized by long, inconsistent intermenstrual intervals and amenorrhea, the most severe menstrual cycle disturbance, which is characterized by the absence of menses for at least 3 months.

estrogen-related factors. Indeed, the influence of low energy availability on bone formation via hepatic suppression of insulin-like growth factor-1<sup>18</sup> and alteration of circulating concentrations of other metabolic hormones known to influence bone health, ie, leptin<sup>37</sup> and peptide YY,<sup>17</sup> compromises bone health.<sup>23</sup> Furthermore, the suppressive effect of low energy availability on the reproductive axis and, consequently, menstrual function, which contributes to decreased serum concentrations of estrogen, causes an upregulation of bone resorption.<sup>16,38</sup>

As such, compromised bone health represents the downstream effects of both low energy availability and menstrual dysfunction. Due to the suppression of bone formation<sup>15,16</sup> and upregulation of bone resorption<sup>15</sup> related to an energy deficit and the increase in bone resorption related to an estrogen deficit,<sup>16,38</sup> it must be noted that low energy availability and menstrual dysfunction demonstrate independent and synergistic effects on bone health. Unlike the other components of the Female Athlete Triad, poor bone health often does not have overt symptoms, and therefore develops silently, unbeknownst to the athlete. As elegantly described in a recent review paper by Gibbs et al,<sup>10</sup> low bone mineral density (BMD) was observed in 0%–15.4% of female athletes when defined as a Z-score  $\leq -2.0$  and 0%–39.8% when defined as a Z-score between  $-1.0$  and  $-2.0$ . Numerous investigators have reported that amenorrheic athletes present with lower BMD than their eumenorrheic counterparts,

particularly at the highly trabecularized lumbar spine,<sup>3,17,39–45</sup> and strong evidence exists that alterations in metabolic and reproductive hormones caused by an energy deficit contribute to the uncoupling of bone metabolism and subsequent low bone mass.<sup>15–17,23</sup>

With the advent of improved imaging techniques and identification of the clinical consequences of low BMD among female athletes, current Triad research has focused extensively on the bone health component, exploring beyond BMD and assessing bone geometry and microarchitecture, the impact of sport type and loading modality on bone health, the factors that are the strongest contributors to poor bone health among female athletes, and stress fractures, which are a clinical outcome of poor bone health. Despite recent important advances in knowledge about bone health among female athletes presenting with one or more components of the Triad, questions without definitive answers remain, particularly pertaining to appropriate treatment strategies for poor bone health among female athletes and whether restoration of optimal bone health is possible among female athletes with low bone mass and/or impaired bone microarchitecture. As such, the purpose of this review is to examine the current state of Triad research related to the third component of the Triad, ie, poor bone health, in an effort to summarize what we know, what we are learning, and what remains unknown. Several investigators have recently published review articles on the current findings, prevalence, and treatment of the Triad as a

whole,<sup>10,46,47</sup> and readers are encouraged to reference these sources for more information about the energy availability and menstrual dysfunction components of the Triad.

## What are the recent discoveries? Bone geometry and microarchitecture of female athletes

To date, the majority of researchers who have assessed Triad-related detriments in bone health have used measurements obtained from dual-photon absorptiometry or dual-energy x-ray absorptiometry (DXA), both of which are two-dimensional imaging techniques.<sup>17,39–45</sup> Although DXA is currently the clinical gold standard for diagnosis of osteopenia and osteoporosis, it is limited by the two-dimensional nature of its areal BMD measurements and is not capable of assessing true BMD, ie, volumetric BMD, or bone geometry.<sup>48</sup> As such, investigators have explored bone health among athletes with Triad perturbations via three-dimensional bone imaging, ie, primarily peripheral quantitative computed tomography (pQCT).<sup>3,49–51</sup> Assessment of bone structure with three-dimensional imaging has revealed deterioration of the trabecular microarchitecture, characterized by lower trabecular number and greater trabecular spacing, at the distal tibia among amenorrheic adolescent and young adult athletes compared with eumenorrheic athletes and nonathletic controls.<sup>3</sup>

Of particular interest, however, is that amenorrheic athletes appear to acquire some of the osteogenic benefits of habitual exercise in that bone size, referred to as total bone area, at the distal tibia is greater among amenorrheic athletes compared with sedentary controls and similar to that observed in eumenorrheic athletes.<sup>3</sup> Because bone strength, or the resistance of bone to bending forces, is equivalent to the cross-sectional radius of the bone to the fourth power,<sup>52,53</sup> bone size is an extremely important and influential component of bone strength. This fact highlights that despite menstrual dysfunction, habitual exercise may be partially protective against a reduction in bone strength that is typical with an energy deficit and menstrual dysfunction. It must be noted, however, that despite the larger total bone area, assessment of the components of total bone, ie, trabecular and cortical bone, reveals that amenorrheic athletes have a greater relative trabecular area (% of the total area) but a smaller relative cortical area at the distal tibia compared with sedentary controls.<sup>3,49</sup> These results suggest that, despite the larger bone size, the thickness of the cortical shell and, therefore, mineralization of the cortical bone, may be compromised in amenorrheic athletes compared with nonathletic controls.<sup>49</sup>

In a slightly different model consisting of retired elite gymnasts (mean age 22.3 years) grouped according to history of amenorrhea, Ducher et al<sup>50</sup> demonstrated that the bone strength index, a measure of the bone's resistance to compressive forces, at the distal radius was significantly lower among retired gymnasts with a history of amenorrhea compared with retired gymnasts without a history of amenorrhea. On the other hand, there was a trend ( $P < 0.09$ ) towards a greater strength strain index, a measure of resistance against bending and torsional forces,<sup>54–56</sup> at the proximal tibia among retired gymnasts with a history of amenorrhea compared with retired gymnasts without a history of amenorrhea.<sup>50</sup> As such, it appears that, among amenorrheic athletes, areas of bone with a greater trabecular content, such as distal sites, may be more susceptible to decrements in strength compared with proximal sites that are composed primarily of cortical bone and are perhaps more sensitive to changes in bone geometry, ie, increases in bone size, initiated from muscle and gravitational forces during habitual exercise.

Although pQCT, unlike DXA, allows for the estimation of bone strength, it is primarily used in research settings and therefore has limited clinical availability.<sup>53</sup> For this reason, algorithms that have been developed for DXA to estimate bone geometry at the hip have provided a clinically-useful alternative to three-dimensional imaging techniques.<sup>57–59</sup> Recent assessment of hip geometry using DXA in athletes grouped according to menstrual status revealed that the cross-sectional area of the femoral neck and shaft was significantly smaller in oligo/amenorrheic athletes compared with eumenorrheic athletes but similar to that observed in nonathletes.<sup>60,61</sup> Unlike peripheral measurements of bone area,<sup>3</sup> these results suggest that bone geometry at the femoral neck, a common site of osteoporotic fracture<sup>62</sup> and a potential site for debilitating stress fractures,<sup>63</sup> may be compromised by menstrual dysfunction. It must be noted, however, that this difference in cross-sectional area was lost after adjusting for lean body mass,<sup>60</sup> and other investigators have observed no difference in femoral neck cross-sectional area between amenorrheic and eumenorrheic athletes.<sup>45</sup>

## Sport loading modality, bone health, and menstrual status

In light of the aforementioned findings regarding bone structure, the strong influence of sport loading modality must not be overlooked. Findings from several investigations conducted by Nikander et al<sup>64–67</sup> have demonstrated that female athletes who participate in high impact and odd impact sports present with favorable bone characteristics that are not

observed among nonathletic referents and athletes participating in nonimpact sports such as swimming and cycling. For example, healthy premenopausal athletes of high impact (volleyball, hurdling), odd impact (soccer, speed skating, step aerobics, squash), high magnitude (weightlifting), and repetitive low impact (orienteering, cross-country skiing) sports present with significantly greater areal BMD and estimated cross-sectional area of the femoral neck compared with nonathletic controls; whereas, swimmers and cyclists demonstrate no difference in these parameters compared with the referents.<sup>64</sup> It must also be noted that athletes in the high-impact and odd-impact groups appear to reap the greatest skeletal benefits from loading at the femoral neck, with an increase above the referent group of 19.9%–28.7% for areal BMD and 18.0%–26.5% for cross-sectional area compared with an increase of 14.2% and 11.9% for areal BMD and cross-sectional area, respectively, for athletes in the repetitive low-impact group.<sup>64</sup> Muscle performance-related joint moment and loading modality, ie, high impact, odd impact, and nonimpact, are among the strongest predictors of bone structure and estimated bone strength at the tibia, radius, and humerus among women,<sup>65</sup> highlighting the important contributions of muscle forces and sport type, which are intricately linked, to bone health and fracture risk among female athletes.

As such, female athletes with low energy availability and menstrual dysfunction represent a unique environment for bone health due to the opposing actions of habitual physical activity and suppressed metabolic and reproductive environments on bone quantity (mass) and quality (structure). Interestingly, habitual physical activity may have a protective effect on weight-bearing bones such as the femur and tibia in amenorrheic athletes, or at least attenuate the detrimental effects of a poor metabolic and reproductive environment on bone health; however, the protective effect may be lost at nonweight-bearing sites such as the lumbar spine and radius.<sup>3,43</sup> Among adolescent and young adult female athletes who primarily participate in aerobic weight-bearing training of the legs, running, or other endurance training, the BMD Z-score at the lumbar spine is significantly lower among amenorrheic athletes than in eumenorrheic athletes and sedentary controls;<sup>3,43</sup> however, BMD Z-scores at the femoral neck and hip are lower than their eumenorrheic counterparts but similar to sedentary controls,<sup>3,43</sup> suggesting that the loss or failure to accrue bone mass at the weight-bearing femur is attenuated by habitual physical activity. Further, amenorrheic athletes demonstrate greater total and trabecular bone area at the distal tibia compared

with sedentary girls and women, a difference that is lost at the distal radius.<sup>3</sup>

It is imperative to note, however, that the response of bone mass and structure to the antithetical influence of habitual exercise and exercise-associated menstrual dysfunction may be dependent on the type of activity that is regularly performed by the athletes. To date, one study has explored the combined influence of loading modality and menstrual status on bone health in female high school athletes.<sup>68</sup> The athletes were categorized as eumenorrheic or oligo/amenorrheic and were separated into two groups according to sport type, including repetitive/nonimpact sports (distance running and swimming) and high/odd impact sports (soccer, softball, volleyball, lacrosse, tennis, track sprinters, and jumpers).<sup>68</sup> Among regularly-menstruating athletes, those participating in high/odd impact sports demonstrated significantly greater hip BMD compared with repetitive/nonimpact athletes.<sup>68</sup> Similarly, among oligo/amenorrheic athletes, lumbar spine Z-score was significantly greater among those participating in high/odd impact sports compared with those participating in repetitive nonimpact sports.<sup>68</sup> Further, lumbar spine BMD (both absolute BMD and Z-score) was significantly greater in eumenorrheic, high/odd impact athletes than in oligo/amenorrheic, repetitive/nonimpact athletes.<sup>68</sup> No differences in absolute BMD or Z-score were observed between athletes of differing menstrual status (eumenorrheic versus oligo/amenorrheic) who were participating in sports of a similar loading modality.<sup>68</sup> These results confirm previous reports of the strong influence of sport loading modality on the BMD of athletes,<sup>64–67</sup> yet also reveal that menstrual status may not strongly discriminate among athletes participating in sports of similar loading modality. Rather, the largest differences may be observed when loading modality and menstrual status are combined, such that those athletes participating in the most osteogenic activities and presenting with the most regular menstrual cycles demonstrate greater bone mass than athletes who participate in less osteogenic sports and present with irregular or absent menstrual cycles.

## Primary contributors to bone mass and structure in female athletes

As previously mentioned, amenorrheic athletes frequently present with low areal BMD at the lumbar spine,<sup>3,17,39–45</sup> reduced trabecular volumetric BMD and bone strength index at the distal radius,<sup>50</sup> and deterioration of the trabecular microarchitecture at the distal tibia<sup>3</sup> when compared with their eumenorrheic counterparts. Taken together, these results suggest that sites of primarily trabecular bone



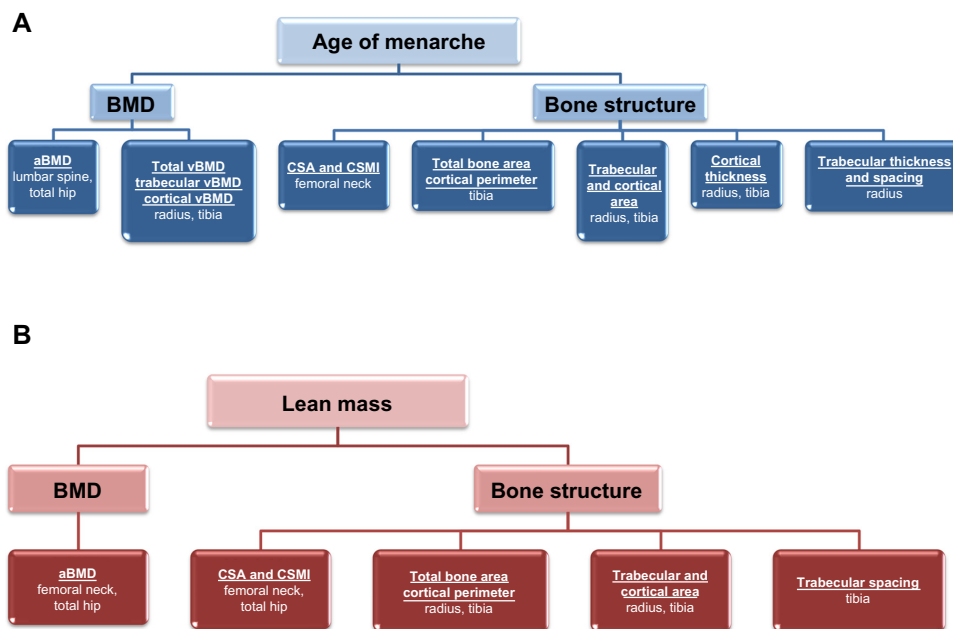
are sensitive to changes in the hormonal environment and therefore are susceptible to poor bone quantity (mass) and quality (structure) and, subsequently, increased fracture risk. In fact, a cross-sectional analysis of amenorrheic and eumenorrheic exercising women revealed that upon consideration of reproductive function, metabolic hormones, and body composition, the strongest predictors of lumbar spine areal BMD were markers of reproductive function, ie, mean estrogen concentration during a menstrual cycle and age of menarche, which together explained 25.5% of the variance in areal BMD at this site.<sup>45</sup> Lean body mass was the strongest predictor of areal BMD and estimated geometry at weight-bearing sites, explaining 8.5%–34.8% of the variance in areal BMD and estimated geometry at the femoral neck and total hip.<sup>45</sup> Notably, the metabolic hormone, leptin, was also a significant predictor of femoral neck cross-sectional area.<sup>45</sup> These results demonstrate the importance of energy availability and therefore metabolic status, body mass, and menstrual function on bone health, including both densitometric and geometrical variables, which are two important components of bone strength. Further, age of menarche was a significant predictor of both areal BMD and bone geometry at the lumbar spine and hip region, highlighting the importance of estrogen exposure during adolescence for BMD and bone geometry, and therefore bone strength, during adulthood.<sup>45</sup>

In fact, the influence of age of menarche on BMD must not be underestimated. In adolescent girls, bone mineral accrual occurs rapidly between the ages of 11 and 14 years<sup>69,70</sup> and slows drastically after the age of 16 years.<sup>69</sup> Further, the majority of peak bone mass is attained by the age of 18 years.<sup>38,71,72</sup> Consequently, the optimal window to accrue bone mass may be missed or compromised in the case of late menarche, defined as the onset of menses occurring at age 15 years or older.<sup>27</sup> Optimal accrual of bone mineral and attainment of a healthy peak bone mass are dependent on normal endocrine function which includes, but is not limited to, adequate circulating concentrations of sex steroids.<sup>38,72</sup> Because adolescence represents a critical window for gains in bone mass, adolescent athletes who experience primary and/or secondary amenorrhea may be at risk for worse skeletal consequences than adult athletes who are currently presenting with secondary amenorrhea but have a history of regular menses during adolescence.

In an elegant analysis of a large sample of exercising adolescent girls and young adult women, late menarche was one of the strongest predictors of low BMD ( $Z$ -score  $< -1$  and  $\leq -2$ ).<sup>73</sup> In addition, lean sport participation and lean body mass, after adjusting for body mass index, menstrual

status, dietary restraint status, and age, were also significant predictors of low BMD ( $Z$ -score  $< -1$  and  $\leq -2$ ).<sup>73</sup> Furthermore, adolescents and women with late menarche were four times more likely to have low BMD.<sup>73</sup> An additional concern is that 55.2% and 13.8% of the girls and women with late menarche had low BMD as defined by a  $Z$ -score  $< -1$  and  $\leq -2$ , respectively.<sup>73</sup> Other Triad risk factors that were associated with low BMD in this sample included the presence of oligo/amenorrhea, low body mass index, and low body weight, such that those presenting with these risk factors were 2–5 times more likely to demonstrate low BMD.<sup>73</sup>

A closer look at bone type and structure confirms the importance of age of menarche and lean mass for bone health and perhaps provides a glimpse into the underlying mechanism that explains the aforementioned influence of age of menarche and lean mass on DXA-derived areal BMD and bone geometry. Among a sample of adolescent athletes of varying menstrual status and nonathletic controls, age of menarche, bone age, lean mass, and menstrual/athletic status were entered into a model to identify significant determinants ( $P < 0.05$ ) of volumetric BMD and bone structure.<sup>3</sup> Age of menarche was a significant predictor of trabecular and cortical volumetric BMD, trabecular and cortical area, and cortical thickness at the radius and tibia.<sup>3</sup> Further, trabecular microarchitecture at the radius, including trabecular thickness and trabecular spacing, was determined by age of menarche.<sup>3</sup> Lean mass, on the other hand, was a significant predictor of cortical and trabecular area at the radius and tibia in addition to total area and cortical perimeter at both sites.<sup>3</sup> Further analysis of the influence of age of menarche and lean mass on bone health revealed that both factors were significant predictors of stiffness and failure load at both the radius and tibia.<sup>49</sup> Figure 3 provides a summary of the parameters of BMD and bone structure that are predicted by age of menarche and lean mass.<sup>3,45</sup> In sum, a surrogate marker of reproductive status, ie, age of menarche, is a significant predictor of densitometric, structural, and microarchitectural variables, emphasizing the importance of optimal menstrual status during the critical adolescent window. Lean mass, on the other hand, is primarily a significant predictor of variables pertaining to bone size and area. Together, these results demonstrate the inextricable link between conditions of the Triad, specifically the detrimental impact that low energy availability, which typically leads to low body weight and menstrual dysfunction characterized by either primary or secondary amenorrhea, has on bone health.



**Figure 3** Strong predictors of bone mineral density and bone structure in exercising women according to recent investigations.

**Notes:** (A) Parameters of bone mineral density and bone structure that are predicted by age of menarche. (B) Parameters of bone mineral density and bone structure that are predicted by lean mass. Data from Ackerman et al<sup>3</sup> and Mallinson et al.<sup>45</sup>

**Abbreviations:** aBMD, areal bone mineral density; vBMD, volumetric bone mineral density; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia.

## Stress fractures

Stress fractures are often a clinical manifestation of low bone mass.<sup>4</sup> These debilitating injuries occur as a result of an accumulation of microcracks under conditions of repetitive activities such as distance running, inadequate rest, or poor nutrition.<sup>74</sup> The development of microcracks within bone is a normal part of the continual remodeling process,<sup>74</sup> and these microcracks develop as a result of repeated force on bone through loading.<sup>74</sup> Subsequently, osteoclasts resorb the area of bone with the microcracks, and osteoblasts form new bone at the site.<sup>74</sup> However, in the event of the aforementioned conditions, appropriate healing of microcracks may not be realized with inadequate rest and/or altered bone metabolism, ie, increased bone resorption and decreased bone formation, as is evident in an energy-deficient state.<sup>15,16,74</sup> Stress fractures are characterized by pain and lost training time,<sup>75,76</sup> and can lead to serious health consequences such as complete fracture and malunion or disunion of the bone, thereby requiring surgery and prolonging healing time, if not identified and treated in a timely manner.<sup>63,76</sup> As clearly outlined in a published case study of an adolescent runner who experienced a displaced femoral neck fracture while competing, lack of appropriate treatment of these injuries has significant implications and can lead to long-term consequences including, but not limited to, reduced mobility, limited participation in sports, and poor healing.<sup>63</sup>

In a 5-year prospective analysis of collegiate track and field and cross-country athletes (n=211), 16% of athletes

sustained a bone stress injury.<sup>77</sup> Of these injured athletes, the majority (65%) were female, a finding that agrees with the observations of other investigators.<sup>78–80</sup> Factors associated with the Female Athlete Triad have also been observed to be significant predictors of stress fracture risk,<sup>4,77,81</sup> perhaps serving as one underlying reason, among several potential reasons, for the comparatively greater prevalence of stress fractures in women compared with men. Analysis of several Triad risk factors in a large sample of female athletes (n=259) revealed that low BMD (Z-score < -1), participation in  $\geq 12$  hours of purposeful exercise per week, and body mass index < 21.0 kg/m<sup>2</sup> were observed more frequently among female athletes with a physician-diagnosed bone stress injury (14.7%–21.0%) compared with noninjured athletes (3.4%–7.6%).<sup>4</sup> Furthermore, female athletes who presented with any of these three Triad risk factors were 2.4–4.9 times more likely to sustain a bone stress injury, and the combination of all three increased the risk of injury by 6.8-fold.<sup>4</sup> In a sample of female runners and triathletes, a higher prevalence of oligo/amenorrhea was observed among athletes with a history of stress fracture compared with athletes without a history of fracture.<sup>81</sup> Furthermore, the athletes who reported current oligo/amenorrhea were 4.7 times more likely to experience a stress fracture compared with eumenorrheic athletes.<sup>81</sup> Not only are athletes with menstrual dysfunction at higher risk for stress fracture, but they may also be at risk for more severe stress fractures.<sup>77</sup> Stress fracture diagnosis

via magnetic resonance imaging revealed that female athletes with oligo/amenorrhea suffered more severe stress fractures and more stress injuries at trabecular bone sites (versus cortical bone sites) when compared with eumenorrheic athletes.<sup>77</sup> Notably, stress injuries of greater severity and at trabecular bone sites demonstrated longer recovery and time to full return to sport compared with less severe injuries and those injuries occurring at cortical bone sites.<sup>77</sup> In sum, these results provide further evidence of the inextricable link among components of the Triad, ie, the robust influence of low energy availability and menstrual dysfunction on bone health, and the clinical consequences that can flow from the Triad if symptoms are left unnoticed or ignored.

## What remains unknown?

### Does reversal of low energy availability and menstrual dysfunction among athletes with the Triad allow for complete recovery of bone health?

Research conducted to date has clearly established that bone health is compromised in an energy-deficient and estrogen-deficient environment. What is unclear, and is perhaps the more important question, is the extent to which bone health, including both bone quantity (bone mass) and bone quality (bone structure), can be recovered with improvements in the energetic and reproductive environments in affected girls and women. Exploration of the reversal of low bone mass among female athletes or recreationally active women experiencing menstrual dysfunction has been limited to case studies<sup>82–84</sup> and follow-up investigations<sup>85–89</sup> (Table 1). However, studies in a similar but more severe model of energy deficiency, ie, anorexia nervosa, provide interesting perspectives on the question.<sup>90–93</sup>

Published case studies of endurance athletes with amenorrhea and, frequently, low BMD demonstrated increases in hip and spine areal BMD of 0.8%–25.5% after weight gain and over the course of 3–8 years.<sup>82,83</sup> Likewise, although a 12-month intervention of increased caloric intake designed to improve energy status in two recreationally active, young amenorrheic women demonstrated no clinically significant increase in areal BMD, a 50% increase in markers of bone formation was observed, suggesting that a clinically significant increase in areal BMD may have occurred with an intervention of longer duration.<sup>84</sup> Similarly, in female athletes who were monitored for 1.3–5 years, an increase in lumbar spine areal BMD or Z-score was observed in amenorrheic athletes who gained weight<sup>86,87</sup> or fat mass<sup>89</sup> and, for the majority,

also resumed menses.<sup>86,87,89</sup> Importantly, the BMD of these athletes did not normalize to that of regularly-menstruating athletes during the 15–24-month follow-up period.<sup>86,87,89</sup> These results are in agreement with an 8-year follow-up investigation that revealed persistently low lumbar spine areal BMD in formerly amenorrheic and oligomenorrheic athletes who had experienced regular menstrual cycles and/or used oral contraceptives for several years.<sup>85</sup> It must be noted that all but one of these follow-up studies<sup>85,86,89</sup> solely included exercising, young adult women. In the one study that included adolescent athletes,<sup>87</sup> the mean age of the study population at baseline was 22.2 years due to the large age range of the study participants (13–29 years). Given the importance of adequate estrogen concentrations during the adolescent years for optimal bone mineral accrual and attainment of a healthy peak bone mass,<sup>38,72</sup> it is possible that recovery of bone health in athletes with amenorrhea during adolescence (ie, primary and/or secondary amenorrhea) versus athletes with amenorrhea during young adulthood (secondary amenorrhea with regular menses during adolescence) may be different. The time course of the reversal of energy availability and menstrual dysfunction during adolescence or adulthood most likely plays a role in successful recovery of bone health.

To date, there are no studies that have followed adolescent athletes with primary amenorrhea/late menarche through their third decade of life, assessing BMD at regular intervals and comparing it with the BMD of both regularly menstruating athletes and nonathletic controls, to determine if bone mineral accrual will continue later in life in athletes with late menarche, provided that optimal energy availability and menstrual function is restored. Furthermore, there have been no reports of interventions designed to reverse the energy and estrogen deficiency in amenorrheic female athletes, with the long-term goal of improving bone health. In our laboratory, a prospective, randomized controlled trial is underway examining the effects of increased caloric intake on recovery of menstrual function and bone health in exercising women with exercise-associated menstrual disturbances. Results from this trial will be reported in the literature in the future. Such studies, however, have been undertaken in the anorexic population, and will be discussed here.

In girls and women with anorexia nervosa, nonpharmacological approaches to treatment that have resulted in weight gain concomitant with resumption of menses have contributed to annual increases in lumbar spine and hip areal BMD of 3.1% and 1.8%, respectively.<sup>90</sup> Furthermore, anorexic girls who gained weight and resumed menses did not demonstrate further decreases in lumbar spine



Table 1 Summary of changes in BMD among amenorrheic athletes who gained weight and/or resumed menses

Reference	Participants			Duration of follow-up	Change in body weight or BMI	Results	
	Sample	Age (years)	BMI (kg/m <sup>2</sup> )			Resumption of menses	Change in BMD
<b>Case reports</b>							
Zanker et al <sup>83</sup>	Triathlete with primary amenorrhea	24.8	16.3	12 years	+8.1 kg over 3 years	N/A; OCs	LS: +0.8% over 3 years Hip: +16.9% over 3 years
Fredericson and Kent <sup>82</sup>	Distance runner with primary amenorrhea	22.9	15.8	8 years	+16.9 kg	OCs for 5 years followed by regular menstrual cycles for 3 years	LS: +25.5% Hip: +19.5%
Mallinson et al <sup>84</sup>	Two female athletes with secondary amenorrhea	19	20.4	12 months	+4.2 kg	74 days into intervention	LS: +0.8% FN: -4.3% Hip: -2.0%
		24	19.7		+2.8 kg	23 and 144 days into intervention	LS: +2.0% FN: +1.4% Hip: +1.9%
<b>Follow-up studies</b>							
Drinkwater et al <sup>86</sup>	7 AA	26.7±2.1**	19.9	15 months	+1.9 kg	4.7 months after baseline	LS: +6.3%
	7 EA	26.9±2.5**	20.6		-0.2 kg	N/A	LS: -0.3%
Jonnavithula et al <sup>87</sup>	5 AA	20.4±5.7*	NR	2 years	+5.4 kg	Resumed, n=3	LS: +13.3%
	12 EA	23.5±5.1*	NR		-0.2 kg	N/A	LS: +3.2%
Keen and Drinkwater <sup>85</sup>	11 O/A	30.3±1.8**	19.1±0.5**	6-10 years	1.1 kg	Resumed, n=6 OCs, n=4 Amen, n=1	No change relative to R/R group; BMD remained significantly below R/R group and R/O/A group for LS and FN, respectively
	9 R/O/A	31.4±1.7**	20.3±0.6**		+0.5 kg	R, n=6 OCs, n=3	No change relative to R/R group
Warren et al <sup>88</sup>	9 R/R	31.0±1.1**	20.1±0.4**		+4.6 kg	N/A	N/A
	10 AA	NR	NR	2 years	NR	Resumed, n=3	LS: +12.0%
	17 EA	NR	NR		NR	N/A	LS: +2.3%
Hind et al <sup>89</sup>	12 AA	22.0±3.6*	18.1±1.0*	5 years	+1.8 kg/m <sup>2</sup>	Resumed; n=10	LS Z-score: ↑ from -1.5 to -0.9 Hip Z-score: ↑ from 0.3 to 0.6
	6 EA	27.4±3.3*	19.0±1.2*		+0.8 kg/m <sup>2</sup>	N/A	LS Z-score: ↑ from -0.1 to 0.2 Hip Z-score: no change from 0.7

**Notes:** \*mean±SD; \*\*mean±SE

**Abbreviations:** BMD, bone mineral density; OCs, oral contraceptives; LS, lumbar spine; FN, femoral neck; AA, amenorrheic athlete; EA, eumenorrheic athlete; O/A, had always been and were currently oligomenorrheic or amenorrheic; R/O/A, regularly menstruating with episodes of amenorrhea or oligomenorrhea; R/R, had always menstruated regularly; R, regularly menstruating at baseline and remained regularly menstruating during follow-up; Amen, amenorrheic at baseline and remained amenorrheic during follow-up; N/A, not applicable; NR, not reported.

areal BMD.<sup>91</sup> Interestingly, beneficial bone health outcomes may be observed as a result of weight gain and resumption of menses that occur independently rather than concomitantly. For example, both spine<sup>92,93</sup> and hip<sup>90,93</sup> areal BMD increased in anorexic women who gained weight independent of resumption of menses. Conversely, a significant increase in lumbar spine areal BMD was observed in anorexic women who resumed menses without concomitant weight gain.<sup>90</sup> As such, a nonpharmacological approach that focuses on increased energy intake with the goals of weight gain and resumption of menses has the potential to be an effective treatment strategy among athletes with low BMD caused by the synergistic effects of energy deficiency and estrogen deficiency.

## **What is the most appropriate and effective treatment for low bone mass and compromised bone structure in female athletes with the Triad?**

### **Nonpharmacological treatment**

The nonpharmacological approach of an increase in caloric intake, a decrease in energy expenditure, or both in order to promote weight gain and resumption of menstrual function is the first goal of treatment for the Triad. This strategy is the first approach to treatment since the initial source of the Triad, ie, low energy availability, can only be addressed by increasing energy availability.<sup>2,94</sup> As previously highlighted, improvements in areal BMD of 1%–26% and bone metabolism of 50% were observed with weight gain and resumption of menses, both independently and concomitantly, among case studies of female athletes,<sup>82–84</sup> suggesting that a nonpharmacological approach may be effective. However, conclusions about effectiveness cannot be drawn due to the lack of controlled prospective interventions. More research is necessary to determine the time course of changes in BMD and bone structure in conjunction with weight gain and resumption of menses and the specific nutritional intervention that is most effective for improving BMD and bone microarchitecture in athletes with Triad-related decrements in bone health.

In conjunction with nonpharmacological treatment, adequate intakes of calcium (1,000–1,300 mg/day)<sup>95,96</sup> and vitamin D (600–1,000 IU/day)<sup>95–97</sup> are also important for bone mineralization.<sup>2</sup> Although intake of these nutrients should ideally come from calcium-rich foods, supplementation may be necessary to provide adequate amounts of these micronutrients.<sup>2</sup>

An additional nonpharmacological treatment approach to be considered is participation in resistance training and/or weight-bearing exercise, which are both established to be osteogenic, particularly when the weight-bearing activity involves high ground reaction forces and/or heterogeneous and uncustomary patterns of loading.<sup>64–67</sup> Although energy expenditure and intake must be closely monitored with the addition of this component to prevent reinitiation of an energy-deficient state, the gain in lean mass that may accompany resistance training<sup>98</sup> and the skeletal adaptations that may accompany high impact or odd impact weight-bearing exercise<sup>64–67</sup> may be beneficial for improvements in bone health. However, caution must be exercised when implementing high-impact activity in female athletes with low BMD due to the potential for fracture.<sup>99</sup>

Among exercising women, lean mass has been demonstrated to be a strong predictor of bone mass and geometry.<sup>3,45</sup> Prospective evaluation of skeletal recovery in anorexic women for 6–69 months revealed that percent change in fat-free mass was a significant positive predictor of the change in hip and lumbar spine areal BMD.<sup>90</sup> Furthermore, lean mass was a significant predictor of change in femoral shaft cross-sectional area from the age of 17–21.5 years among female adolescents,<sup>100</sup> suggesting that an increase in lean mass may aid improvement in bone strength and reduced risk for fracture.

### **Pharmacological treatment**

The primary pharmacological agents that have been investigated to improve low bone mass in women with functional hypothalamic amenorrhea, including both athletes and anorexic women, encompass traditional treatments such as combined oral contraceptives (COC)<sup>101–115</sup> and estrogen therapy,<sup>112,116–122</sup> and more novel treatments such as androgens,<sup>105,123–125</sup> recombinant human insulin-like growth factor-1<sup>106</sup> and leptin,<sup>29,37,126</sup> and bisphosphonates.<sup>125,127,128</sup> In 2008, a thorough systematic review outlined current pharmacological treatments for low bone mass in women with functional hypothalamic amenorrhea and described in detail the efficacy of various treatments based on published reports from 1960 to 2007.<sup>129</sup> Readers are encouraged to refer to this review paper for an overview of studies on this topic dating to 2007. In this paper, we aim to provide an update on the current state of pharmacological treatment for low bone mass in female athletes based on research that has been published since 2007. The majority of published studies to date that describe the impact of pharmacological treatment on low bone mass in amenorrheic women have been conducted in the

anorexic population, highlighting the need for more research in this area, specifically among female athletes.

### Combined oral contraceptives

As of 2007, 13 studies including randomized controlled trials (n=6),<sup>102–107</sup> cohort studies (n=2),<sup>108,109</sup> prospective studies (n=4),<sup>110–113</sup> and one cross-sectional study<sup>114</sup> have explored the impact of treatment with COC on bone mass in women with functional hypothalamic amenorrhea. Six of these studies were conducted in athletes with functional hypothalamic amenorrhea,<sup>102–104,108,109,113</sup> and seven were conducted in anorexic women or adolescents.<sup>105–107,110–112,114</sup> Results from the six studies in athletes with functional hypothalamic amenorrhea<sup>102–104,108,109,113</sup> and one study in anorexic women<sup>114</sup> demonstrated that COC had a beneficial impact on BMD; however, results from the remaining six studies,<sup>105–107,110–112</sup> which were all conducted in anorexic women or adolescents, indicated no effect of COC on BMD.<sup>129</sup> These results highlight the equivocal nature of the efficacy of COC in improving bone health among women with functional hypothalamic amenorrhea associated with exercise or anorexia.<sup>129</sup>

Recent reports of the effect of treatment with COC on bone mass in female athletes with exercise-associated functional hypothalamic amenorrhea are limited to one randomized controlled trial. In an intention-to-treat analysis, Cobb et al<sup>101</sup> observed no effect of treatment with COC on areal BMD or bone mineral content at the lumbar spine in competitive female runners. It must be noted, however, that both the COC group and the control group included eumenorrheic, oligomenorrheic, and amenorrheic athletes.<sup>101</sup> A subanalysis of the amenorrheic athletes alone revealed that athletes in the COC treatment group and those in the control group demonstrated a significant increase in areal BMD at the lumbar spine, again indicating the absence of a treatment effect in amenorrheic athletes.<sup>101</sup>

### Estrogen therapy

Prior to 2007, six studies, including randomized controlled trials (n=2),<sup>116,117</sup> and retrospective (n=1),<sup>118</sup> prospective (n=1),<sup>112</sup> cross-sectional (n=1),<sup>119</sup> and case studies (n=1),<sup>120</sup> investigated the impact of estrogen therapy on bone mass in women with functional hypothalamic amenorrhea associated with either exercise (n=3)<sup>116–118</sup> or anorexia nervosa (n=3).<sup>112,119,120</sup> Similar to the results for COC treatment, half of the studies (n=3)<sup>118–120</sup> demonstrated that estrogen therapy had a beneficial impact on BMD; whereas, the other half (n=3)<sup>112,116,117</sup> showed no positive effect of estrogen therapy on BMD.<sup>129</sup>

No recent studies have been published exploring the impact of estrogen therapy on BMD in female athletes. Recently published results of the effect of estrogen therapy on BMD in anorexic adolescents or women confirmed the previous equivocal findings.<sup>121,122</sup> Adolescent girls with anorexia who received either transdermal 17 $\beta$ -estradiol (mature girls, n=96) or incremental low-dose oral ethinyl estradiol (immature girls, n=14) for 18 months had a significant increase in lumbar spine and hip areal BMD compared with anorexic girls treated with placebo.<sup>121</sup> On the other hand, in an older population of anorexic patients (mean age 25.3 years) presenting with osteoporosis, treatment with 17 $\beta$ -estradiol for 2 years did not result in a significant increase in areal BMD at any site and the change in areal BMD was not different than the change observed in the nontreated group.<sup>122</sup>

These recent results for both COC and estrogen therapy in women with functional hypothalamic amenorrhea are in agreement with the conclusions drawn from a meta-analysis that explored the influence of estrogen preparations on bone health in young women with anorexia nervosa.<sup>130</sup> Although treatment with estrogen preparations in anorexic women appears to result in attenuated bone loss at the lumbar spine (but not femoral neck) when compared with those not receiving treatment, the evidence is weak, thereby confirming the inconclusive influence of COC or estrogen therapy on bone health in anorexic women. These results are in contrast with the mean 2.5% annual increase in areal BMD among anorexic women who gained weight and resumed menses,<sup>90</sup> highlighting the importance of nutritional interventions that result in weight gain and resumption of menses in order to improve bone health in energy-deficient and estrogen-deficient populations.<sup>130</sup>

### Androgen therapy

As of 2007, androgen therapy had only been investigated in anorexic women. Although favorable changes in bone turnover markers occurred following androgen therapy,<sup>105,123,124</sup> no significant improvements in BMD were observed.<sup>105</sup> In agreement with the findings of Gordon et al,<sup>105</sup> administration of testosterone to young anorexic women for 12 months had no beneficial effect on BMD.<sup>125</sup> To date, the efficacy of androgen therapy for improving low bone mass in female athletes as a result of the Triad has not been explored.

### Recombinant human insulin-like growth factor-I

Research conducted prior to 2007 demonstrated that administration of recombinant human insulin-like growth

factor-1 appeared to effectively increase lumbar spine areal BMD in anorexic women when used in combination with COC,<sup>106</sup> most likely due to the synergistic effects of an anabolic therapy combined with an antiresorptive therapy. However, this combined therapy only increased BMD by 1.8% in 9 months.<sup>106</sup> Such an approach weakly mimics the goals of a nonpharmacological approach to the Triad by improving circulating concentrations of insulin-like growth factor-1 and increasing bone formation via an improvement in energy status and by inhibiting bone resorption through restoration of adequate circulating concentrations of estrogen secondary to resumption of menses. Recent studies of recombinant human insulin-like growth factor-1 remain limited to the anorexic population, without a specific focus on athletes.<sup>131</sup>

### Recombinant human leptin

Prior to 2007, investigators reported that administration of recombinant human leptin was associated with an increase in markers of bone formation among amenorrheic women;<sup>29</sup> however, the effect of long-term recombinant human leptin treatment on BMD outcomes had not yet been explored. According to a recent study conducted in young women with functional hypothalamic amenorrhea due to strenuous exercise and/or low body weight, 36 weeks of treatment with recombinant human leptin resulted in a significant increase in levels of osteocalcin, a marker of bone formation.<sup>126</sup> Subsequently, an open-label extension of this recombinant human leptin administration study for another 15 months (for a total study duration of 2 years) resulted in a significant increase in lumbar spine areal BMD (range 2.2%–10.8% increase from baseline) among completers (n=4).<sup>37</sup> According to these results, recombinant human leptin appears to be effective for improving BMD; however, it also resulted in weight loss due to the anorexigenic effects of leptin,<sup>37,126</sup> an unfavorable and potentially dangerous outcome in a population of women who most likely need to gain rather than lose weight. As such, recombinant human leptin is not considered a therapeutic option for women with exercise-associated functional hypothalamic amenorrhea.

### Bisphosphonates

Antiresorptive agents known as bisphosphonates are used clinically to treat osteoporosis and osteopenia in postmenopausal women and have been demonstrated to be efficacious in this population.<sup>132,133</sup> However, bisphosphonates have teratogenic effects and stay in skeletal tissue for many years due to their long half-life; therefore, they are

not recommended as a therapeutic option for women with reproductive potential.<sup>134</sup> Furthermore, bisphosphonates may negatively impact skeletal growth during childhood, thereby providing an additional concern for use in adolescent athletes.<sup>134</sup>

Few investigators have explored the efficacy of bisphosphonates in improving bone health in premenopausal anorexic women or adolescents.<sup>125,127,128</sup> Treatment with risedronate for 12 months in anorexic women resulted in a significant increase in posteroanterior lumbar spine areal BMD, lateral spine areal BMD, and hip areal BMD by 3.2%, 3.8%, and 1.9%, respectively, compared with placebo.<sup>125</sup> Anorexic adolescents who received alendronate for 12 months had an increase in areal BMD at the lumbar spine and femoral neck by 3.5% and 4.4%, respectively.<sup>127</sup> This change was significantly different from baseline, but not when compared with the change observed in the control group (2.2% and 2.3%, respectively).<sup>127</sup> The weight gain experienced by both groups during the intervention was the strongest predictor of BMD change, thereby serving as a confounding factor in determining the ability of alendronate to improve bone mass in this population.<sup>127</sup>

To date, however, the impact of bisphosphonates on low bone mass in female athletes with the Triad has not been explored. Case studies of athletes with stress fractures demonstrate that intravenous treatment with bisphosphonates (pamidronate or ibandronate) for 4–8 weeks resulted in alleviation of pain within days<sup>135</sup> to months<sup>136</sup> after the commencement of therapy depending on injury site; in some cases, the athletes were able to resume their training regimen without pain 48–72 hours after the first treatment.<sup>135</sup> However, it must be noted that bisphosphonates are not currently approved by the US Food and Drug Administration (FDA) for use in young, premenopausal athletes with low BMD or fractures;<sup>125,137</sup> therefore, bisphosphonate therapy should only be implemented under the guidance of a specialist in endocrinology or metabolic bone diseases when athletes meet criteria for osteoporosis and are not responding to nonpharmacological treatment.<sup>94</sup>

### Other potential pharmacological agents

In 2002 and 2010, the FDA approved teriparatide (parathyroid hormone [1–34]) and denosumab, respectively, as treatments for osteoporosis in postmenopausal women at high risk for fracture.<sup>138,139</sup> Teriparatide, an anabolic agent unlike the other pharmacological agents currently approved for osteoporosis treatment, stimulates osteoblast action and consequent bone formation by inhibiting osteoblast apoptosis and enhancing

osteoblast formation.<sup>140</sup> Mechanistically, denosumab is an antiresorptive drug that decreases osteoclast action and consequent bone resorption by interfering with the binding of RANKL to its receptor RANK on osteoclasts.<sup>141</sup> The binding of RANKL to RANK, which triggers bone resorption by allowing osteoclast formation and survival,<sup>141</sup> is upregulated with estrogen deficiency due to the indirect relationship between circulating estrogen concentrations and RANKL expression.<sup>141,142</sup> As such, denosumab counteracts the stimulatory effects of estrogen deficiency on bone resorption.<sup>141</sup> Among postmenopausal women, these pharmaceutical agents effectively increase BMD and reduce fracture risk.<sup>143–146</sup>

Teriparatide and denosumab have not yet been studied in female athletes with low bone mass; however, two reports have been published describing the effects of teriparatide on bone mass in premenopausal women.<sup>147,148</sup> Cohen et al<sup>147</sup> observed a significant increase in areal BMD at the lumbar spine, total hip, and femoral neck, and in markers of bone formation during 24 months of teriparatide treatment in premenopausal women with idiopathic low bone mass. Further, transiliac bone biopsies revealed a significant increase in trabecular stiffness and trabecular number and a decrease in trabecular separation following 18 months of treatment with teriparatide.<sup>147</sup> A case report of two women with metatarsal stress fractures demonstrated fracture healing as indicated by formation of a bony callus and radiographic evidence of new bone formation after 4 weeks of teriparatide treatment.<sup>148</sup> Interestingly, in the case of one woman, prior treatment with an immobilizing boot for 6 weeks did not appear to promote much healing, suggesting that teriparatide aided fracture healing.<sup>148</sup> However, these pharmacological therapies are not approved by the FDA for use in premenopausal women with low bone mass; therefore, their administration to young athletes is not recommended.

More research is necessary before a definitive decision can be made regarding optimal treatment for improvement of bone health in athletes suffering from one or more components of the Female Athlete Triad. The research to date suggests that nonpharmacological treatment should be the primary focus since it addresses the root of the problem, and pharmacological therapy should only be considered in special circumstances such as low BMD or a clinically significant fracture with a lack of favorable response to nonpharmacological therapy.<sup>94</sup> Notably, there are currently no FDA-approved treatments for female athletes with low BMD.<sup>137</sup> It is currently unknown how nonpharmacological and pharmacological treatments impact bone geometry and microarchitecture as well as the cortical and trabecular bone

compartments, which are important areas of future research due to the synergistic influence of bone density, bone materials, and bone structure on bone strength,<sup>149–151</sup> and the differing response of trabecular bone versus cortical bone to the energy-deficient and estrogen-deficient environment.<sup>3,49</sup>

## Conclusion

Although often overlooked as a health consequence of low energy availability and menstrual dysfunction due to its silent manifestation, poor bone health in women with the Female Athlete Triad is characterized by detrimental changes in bone density and structure which, ultimately, may lead to clinical endpoints such as osteoporosis and fractures. These clinical consequences may be evident during adolescence or young adulthood when athletes may present with one or more of the Triad components, or may only be perceptible later in life, highlighting the most serious long-term ramification of the Triad. Effective prevention and treatment of the Triad are key factors for optimal health and well-being of female athletes. As such, there is a current need for prospective studies investigating the treatment of low bone mass and compromised bone microarchitecture in female athletes with low energy availability and functional hypothalamic amenorrhea to determine if bone health can be normalized to that of their eumenorrheic counterparts. Results from case studies and follow-up investigations of female athletes, as well as promising results from a non-pharmacological treatment approach focused on improving energy status and menstrual function among the anorexic population, are encouraging and provide the impetus for further exploration of such a strategy to address the low BMD and compromised bone structure found in female athletes with the Triad.

## Disclosure

The authors report no conflicts of interest in this work.

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